R^d is selected from the group consisting of NR^bR^c, OR^a, CO_2R^a, $O(C=O)R^a$, CN, $NR^c(C=O)R^b$, $CONR^aR^c$, $SO_2NR^aR^c$, and a 4-7 membered N-heterocycloalkyl ring that can be optionally interrupted by O, S, NR^c, or C=O;

Y is selected from the group consisting of CR^bR^c, C_{2-6} alkylene and C_{2-6} alkenylene, wherein said alkylene and alkenylene linkers can be optionally interrupted by O, S, or NR^c;

Z is selected from the group consisting of O, S, NR^c, C=O, O(C=O), (C=O)O, $NR^c(C=O)$ or $(C=O)NR^c$;

and the pharmaceutically acceptable salts thereof.

REMARKS

Claims 1-21 are pending in the instant application. Claims 1 has been amended to further define the invention. No new matter has been added. Support for this amendment can be found in the specification at page 10, lines 7-10. Claim 2 has also been amended. No new matter has been added. After entry of the amendments, Claims 1-21 will be pending in the instant application.

Consistent with 37 CFR §1.121, a version of the amended claims with markings to show changes resulting from the above amendments is presented at the end of this response.

Rejection of Claims 1-9 under 35 USC §102(a)

The Examiner has rejected Claims 1-9 under 35 USC §102(a) as being anticipated by Cragoe et al US 6,251,898. Specifically, the Examiner stated that:

> Cragoe et al US '898 teach fluorenone derivatives as recited in the claims. See column 2, lines 5-10, column 9, lines 5 to column 10, line 41. It is also noted that the patentees disclose the claimed products notwithstanding any intended use.

Applicants respectfully traverse this rejection. Applicants have amended the claims. Specifically, Applicants have removed hydrogen from the

definition of R^3 and removed hydroxy, amino, methyl, CF_3, chloro and bromo from the definition of R^4. In light of these amendments, Applicants assert that the claims now clearly fall outside of the disclosure in Cragoe. Thus, the rejection should now be rendered moot. Therefore, Applicants respectfully request the rejection of Claims 1-9 under 35 USC §103(a) be withdrawn.

Rejection of Claims 1-21 under 35 USC §103(a)

The Examiner has rejected Claims 1-21 under 35 USC §103(a) as being unpatentable over Cragoe et al. US 6,251,898 taken with Cragoe et al US 4,604,396. Specifically, the Examiner stated that:

> The Cragoe et al US '898 reference is applied as in the above rejection. Patentees do not expressly teach estrogen receptor modulator use. However, the cited art does teach compounds having similar physical properties and therapeutic effects. See, for example Cragoe et al US '396 column 9, lines 1-45. In light of this one of ordinary skill would have expected similar compounds to have similar effects and as such would not have been unexpected.

Applicants respectfully traverse this rejection.

The present invention claims novel tetrahydrofluorenone derivatives that have use as estrogen receptor modulators. The compounds of the present invention exhibit estrogenic effects through a mechanism that includes binding to the estrogen receptors. This binding is affected by the particular substitution patterns on the tetrahydrofluorenone ring.

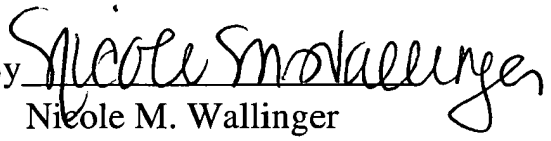
The Cragoe references teach fluorenone derivatives that have use as neuroprotective drugs. The compounds in the Cragoe patents reduce brain edema via an anion transport inhibition mechanism. These compounds are able to regulate the chloride channels in astrocyte cells because of their specific substitution patterns.

The pharmaceutical sciences are highly unpredictable, and it is difficult to predict the level of activity a compound will have in a particular assay merely by looking at it. After reading Cragoe, one would note that substitution

patterns at the 4 and 7 positions appear to affect the activity of the compounds in the brain edema assay. See Cragoe, et al. "Agents for the Treatment of Brain Edema. 2.[(2,3,9,9a-Tetrahydro-3-oxo-9a-substituted-1H-fluoren-7-yl)oxy]alkanoic Acids and Some of Their Analogues," *J. Med. Chem.* **1986** *29*, 825-841 (copy enclosed). After reading these references, one skilled in the art would expect that these compounds might have utility for the treatment of brain edema. One of ordinary skill in the art would expect this type of activity because that is the activity described in the references. However, one of ordinary skill in the art would not expect the compounds described in the Cragoe references to be effective for any other indication than the treatment of brain edema or for anion transport regulation in astrocyte cells. The Cragoe references do not teach the use of fluorenone derivatives for the treatment of estrogen related disorders, and as such one would not be motivated to use the Cragoe compounds for estrogen receptor modulation. Accordingly, because Cragoe does not teach estrogen receptor modulating compounds, one of ordinary skill in the art would not look to the teachings of Cragoe for direction on how to make compounds that can be used as estrogen receptor modulators. Thus, it cannot be said that the estrogen receptor modulating compounds of the present invention could be obvious after reading the Cragoe references. Therefore, Applicants respectfully request the rejection of claims 1-18 under 35 USC §103(a) be withdrawn.

In view of the above amendments and comments, Applicants maintain that the application is in condition for allowance and passage to issue is earnestly requested.

Respectfully submitted,

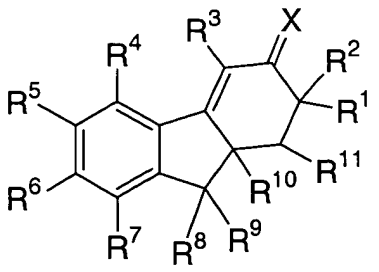
By 

Nicole M. Wallinger
Reg. No. 45,194
Attorney for Applicants
MERCK & CO., INC.
P.O. Box 2000
Rahway, New Jersey 07065-0907
(732) 594-1077

Date: December 04, 2001

VERSION OF AMENDED CLAIMS WITH MARKINGS TO SHOW CHANGES MADE

1. (Amended) A compound of the formula:



wherein X is selected from the group consisting of: O, N-OR^a, N-NR^{a}R^b and C_{1-6} alkylidene, wherein said alkylidene group is unsubstituted or substituted with a group selected from hydroxy, amino, O(C_{1-4}alkyl), NH(C_{1-4}alkyl), or N(C_{1-4}alkyl)$_2$;

R^1 is selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, and C_{2-6}alkynyl, wherein said alkyl, alkenyl and alkynyl groups are either unsubstituted or substituted with a group selected from OR^c, SR^c, NR^{b}R^c ,C(=O)R^c, C(=O)CH_2OH, or phenyl, wherein said phenyl group can either be unsubstituted or substituted with 1-3 substituents independently selected from the group consisting of C_{1-4}alkyl, OH, O(C_{1-4}alkyl), NH_2, NH(C_{1-4}alkyl), NH(C_{1-4}alkyl)$_2$, halo, CN, NO_2, CO_2H, CO_2(C_{1-4}alkyl), C(O)H, and C(O)(C_{1-4}alkyl);

R^2 is selected from the group consisting of hydrogen, hydroxy, iodo, O(C=O)R^c, C(=O)R^c, CO_2R^c, C_{1-6}alkyl, C_{2-6}alkenyl, and C_{2-6}alkynyl, wherein said alkyl, alkenyl and alkynyl groups are either unsubstituted or substituted with a group selected from OR^c, SR^c, NR^{b}R^c ,C(=O)R^c, C(=O)CH_2OH, or phenyl, wherein said phenyl group can either be unsubstituted or substituted with 1-3 substituents independently selected from the group consisting of C_{1-4}alkyl, OH, O(C_{1-4}alkyl),

NH_2, $NH(C_{1-4}alkyl)$, $NH(C_{1-4}alkyl)_2$, halo, CN, NO_2, CO_2H, $CO_2(C_{1-4}alkyl)$, C(O)H, and $C(O)(C_{1-4}alkyl)$;
or R^1 and R^2, when taken together with the carbon atom to which they are attached, form a carbonyl group;
or R^1 and R^2, when taken together, form a C_{1-6} alkylidene group, wherein said alkylidene group is either unsubstituted or substituted with a group selected from the group consisting of hydroxy, $O(C_{1-4}alkyl)$, $N(C_{1-4}alkyl)_2$, and phenyl, wherein said phenyl group can either be unsubstituted or substituted with 1-3 substituents independently selected from the group consisting of $C_{1-4}alkyl$, OH, $O(C_{1-4}alkyl)$, NH_2, $NH(C_{1-4}alkyl)$, $NH(C_{1-4}alkyl)_2$, halo, CN, NO_2, CO_2H, $CO_2(C_{1-4}alkyl)$, C(O)H, and $C(O)(C_{1-4}alkyl)$;

R^3 is selected from the group consisting of ~~hydrogen,~~ fluoro, chloro, bromo, iodo, cyano, NR^aR^c, OR^a, $C(=O)R^a$, CO_2R^c, $CONR^aR^c$, SR^a, $S(=O)R^a$, SO_2R^a, $C_{1-10}alkyl$, $C_{2-10}alkenyl$, $C_{2-10}alkynyl$, $C_{3-7}cycloalkyl$, 4-7 membered heterocycloalkyl, cycloalkylalkyl, aryl, heteroaryl, arylalkyl, and heteroarylalkyl, wherein said alkyl, alkenyl, alkynyl, cycloalkyl, aryl and heteroaryl groups are either unsubstituted or independently substituted with 1, 2 or 3 groups selected from fluoro, chloro, bromo, iodo, cyano, OR^a, NR^aR^c, $O(C=O)R^a$, $O(C=O)NR^aR^c$, $NR^a(C=O)R^c$, $NR^a(C=O)OR^c$, $C(=O)R^a$, CO_2R^a, $CONR^aR^c$, $CSNR^aR^c$, SR^a, $S(O)R^a$, SO_2R^a, $SO_2NR^aR^c$, YR^d, and ZYR^d ;

R^4 is selected from the group consisting of hydrogen, hydroxy, amino, methyl, CF_3, fluoro, chloro, and bromo;

~~R^5 and R^6 are each independently selected from the group consisting of hydrogen, fluoro, chloro, bromo, methyl, amino, OR^b, OR^a, $O(C=O)R^c$, $O(C=O)OR^c$, and $NH(C=O)R^c$;~~

R^5 is selected from the group consisting of hydrogen, fluoro, chloro, bromo, methyl, amino, OR^b, OR^a, $O(C=O)R^c$, $O(C=O)OR^c$, and $NH(C=O)R^c$;

R^6 is selected from the group consisting of hydrogen, fluoro, chloro, bromo, methyl, OR^b, OR^a, $O(C=O)R^c$, and $O(C=O)OR^c$;

R^7 is selected from the group consisting of hydrogen, OR^b, NR^bR^c, fluoro, chloro, bromo, iodo, cyano, nitro, C_{1-6}alkyl, C_{2-6}alkenyl, CF_3, and CHF_2;

R^8 and R^9 are each independently selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, and C_{2-6}alkynyl,
or R^8 and R^9, when taken together with the carbon atom to which they are attached, form a 3-5 membered cycloalkyl ring,
or R^8 and R^9, when taken together with the carbon atom to which they are attached, form a carbonyl group;

R^{10} is selected from the group consisting of hydrogen, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{3-6}cycloalkyl, cycloalkylalkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl, wherein said alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl groups can be optionally substituted with a group selected from chloro, bromo, iodo, OR^b, SR^b, $C(=O)R^b$, or 1-5 fluoro,
or R^{10} and R^1, when taken together with the three intervening carbon atoms to which they are attached, form a 5-6 membered cycloalkyl or cycloalkenyl ring which can be optionally substituted with 1 or 2 groups selected from oxo, hydroxy, or C_{1-6}alkyl;

R^{11} is selected from the group consisting of hydrogen and C_{1-4}alkyl;

R^a is selected from the group consisting of hydrogen, C_{1-10}alkyl, and phenyl, wherein said alkyl group can be optionally substituted with a group selected from hydroxy, amino, $O(C_{1-4}alkyl)$, $NH(C_{1-4}alkyl)$, $N(C_{1-4}alkyl)_2$, phenyl, or 1-5 fluoro, and
wherein said phenyl groups can either be unsubstituted or substituted with 1-3 substituents independently selected from the group consisting of C_{1-4}alkyl, OH, $O(C_{1-4}alkyl)$, NH_2, $NH(C_{1-4}alkyl)$, $NH(C_{1-4}alkyl)_2$, halo, CN, NO_2, CO_2H, $CO_2(C_{1-4}alkyl)$, C(O)H, and $C(O)(C_{1-4}alkyl)$;

R^b is selected from the group consisting of hydrogen, C_{1-10}alkyl, benzyl and phenyl, wherein said phenyl group can either be unsubstituted or substituted with 1-3 substituents independently selected from the group consisting of C_{1-4}alkyl, OH, $O(C_{1-4}alkyl)$, NH_2, $NH(C_{1-}$

4alkyl), NH(C_{1-4}alkyl)$_2$, halo, CN, NO_2, CO_2H, CO_2(C_{1-4}alkyl), C(O)H, and C(O)(C_{1-4}alkyl);

R^c is selected from the group consisting of hydrogen, C_{1-10}alkyl and phenyl, wherein said phenyl group can either be unsubstituted or substituted with 1-3 substituents independently selected from the group consisting of C_{1-4}alkyl, OH, O(C_{1-4}alkyl), NH_2, NH(C_{1-4}alkyl), NH(C_{1-4}alkyl)$_2$, halo, CN, NO_2, CO_2H, CO_2(C_{1-4}alkyl), C(O)H, and C(O)(C_{1-4}alkyl);

or R^a and R^c, whether or not on the same atom, can be taken together with any attached and intervening atoms to form a 4-7 membered ring;

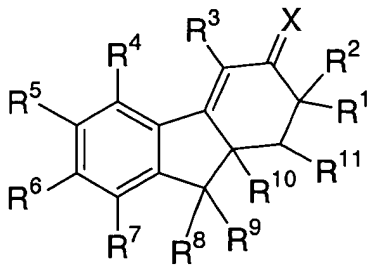
R^d is selected from the group consisting of NR^bR^c, OR^a, CO_2R^a, $O(C=O)R^a$, CN, $NR^c(C=O)R^b$, $CONR^aR^c$, $SO_2NR^aR^c$, and a 4-7 membered N-heterocycloalkyl ring that can be optionally interrupted by O, S, NR^c, or C=O;

Y is selected from the group consisting of CR^bR^c, C_{2-6} alkylene and C_{2-6} alkenylene, wherein said alkylene and alkenylene linkers can be optionally interrupted by O, S, or NR^c;

Z is selected from the group consisting of O, S, NR^c, C=O, O(C=O), (C=O)O, $NR^c(C=O)$ or $(C=O)NR^c$;

and the pharmaceutically acceptable salts thereof.

2. (Amended) A compound of the formula:



wherein X is selected from the group consisting of O and N-OR^a;

R^1 is selected from the group consisting of hydrogen and C_{1-6}alkyl, wherein said alkyl group is either unsubstituted or substituted with a group selected from OR^c or $C(=O)R^c$;

R^2 is selected from the group consisting of hydrogen, hydroxy, iodo, and C_{1-6}alkyl, wherein said alkyl group is either unsubstituted or substituted with a group selected from OR^c or $C(=O)R^c$;

R^3 is selected from the group consisting of ~~hydrogen,~~ chloro, bromo, iodo, cyano, C_{1-10}alkyl, C_{2-10}alkenyl, aryl and heteroaryl, wherein said alkyl, alkenyl, aryl and heteroaryl groups are either unsubstituted or independently substituted with 1, 2 or 3 groups selected from fluoro, chloro, bromo, iodo, cyano, OR^a, NR^aR^c, $C(=O)R^a$, CO_2R^c, $NR^aC(=O)R^c$, $CONR^aR^c$, $CSNR^aR^c$, SR^a, YR^d, and ZYR^d;

R^4 is selected from the group consisting of hydrogen~~;~~ and fluoro, ~~hydroxy and methyl~~;

R^5 and R^6 are each independently selected from the group consisting of hydrogen, fluoro, $O(C=O)R^c$ and OR^a;

R^7 is selected from the group consisting of hydrogen, NR^bR^c, chloro, bromo, nitro and C_{1-6}alkyl;

R^8 and R^9 are each independently selected from the group consisting of hydrogen and C_{1-6}alkyl;
or R^8 and R^9, when taken together with the carbon atom to which they are attached, form a carbonyl group;

R^{10} is selected from the group consisting of hydrogen, C_{1-10}alkyl, C_{2-10}alkenyl, C_{3-6}cycloalkyl and cycloalkylalkyl, wherein said alkyl, alkenyl, cycloalkyl and cycloalkylalkyl groups can be optionally substituted with a group selected from OR^b, SR^b, $C(=O)R^b$, or 1-5 fluoro;
or R^{10} and R^1, when taken together with the three intervening carbon atoms to which they are attached, form a 5-6 membered cycloalkyl ring which can be optionally substituted <u>with</u> C_{1-6}alkyl;

R^{11} is selected from the group consisting of hydrogen and C_{1-4}alkyl;

R^a is selected from the group consisting of hydrogen, C_{1-10}alkyl, and phenyl, wherein said alkyl group can be optionally substituted with a group selected from hydroxy, amino, $O(C_{1-4}alkyl)$, $NH(C_{1-4}alkyl)$, $N(C_{1-4}alkyl)_2$, phenyl, or 1-5 fluoro;

R^b is selected from the group consisting of hydrogen, C_{1-10}alkyl, benzyl and phenyl;

R^c is selected from the group consisting of hydrogen and C_{1-10}alkyl and phenyl;

or R^a and R^c, whether or not on the same atom, can be taken together with any attached and intervening atoms to form a 4-7 membered ring;

R^d is selected from the group consisting of NR^bR^c, OR^a, CO_2R^a, $O(C=O)R^a$, CN, $NR^c(C=O)R^b$, $CONR^aR^c$, $SO_2NR^aR^c$, and a 4-7 membered N-heterocycloalkyl ring that can be optionally interrupted by O, S, NR^c, or C=O;

Y is selected from the group consisting of CR^bR^c, C_{2-6} alkylene and C_{2-6} alkenylene, wherein said alkylene and alkenylene linkers can be optionally interrupted by O, S, or NR^c;

Z is selected from the group consisting of O, S, NR^c, C=O, O(C=O), (C=O)O, $NR^c(C=O)$ or $(C=O)NR^c$;

and the pharmaceutically acceptable salts thereof.